

# Epicardial adipose tissue and atherogenesis: EAT your heart out

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See related paper on page 1635

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Cardiovascular disease (CVD) is increasingly recognized among HIV-infected patients, and carefully performed cohort studies show increased relative risk ratios of 1.5–2.0 [1,2]. Moreover, these studies suggest that traditional risk factors, while accounting for some degree of this increase in relative risk, do not account for all or even a major portion of the increased risk [1]. Insights into the mechanisms of this disease have been forthcoming from imaging studies, in which increased noncalcified plaque has been shown among HIV-infected men and also in HIV-infected women compared with age and BMI-matched controls [3,4]. This observation is significant because noncalcified plaque may be more vulnerable and prone to rupture. In contrast, although calcium score is itself a marker for increased CVD risk, it may represent a process by which plaque becomes more fibrotic and mechanically more stable, and thus, less prone to rupture. Recent studies assessing detailed measures of plaque morphology take these observations one step further and suggest that HIV-infected patients (men in this instance), demonstrate increased features of high-risk morphology plaque, including positive remodeling and low attenuation, fatty lesions [5]. In prior studies, traditional risk factors, such as age, hypertension, cholesterol and Framingham score, were shown to segregate more with calcified plaque, and non-traditional risk factors, such as increased immune activation indices (sCD163 and sCD14), with noncalcified plaque and high-risk morphology plaque [3,5]. Moreover, recent studies suggest increased arterial inflammation in HIV-infected patients, a reflection of macrophage infiltration,

which may provide fertile ground for the development of high risk morphology plaque and increased propensity for plaque rupture [6]. Taken together, these studies and many others suggest that immune activation and other as yet unknown factors may contribute to the development of increased noncalcified plaque, even among those with well treated HIV. The presence of noncalcified plaque with high-risk morphology may contribute to the recent observation of increased rates of sudden cardiac death in HIV-infected patients [7].

In recent years, focus has turned to the epicardial adipose tissue (EAT) as a depot of ectopic adipose tissue, which may share the same embryonic origin as abdominal visceral adipose tissue (VAT). Via secretion of cytokines and other paracrine factors, EAT may contribute to atherogenesis in juxtaposed coronary artery segments. Alternatively, common factors may contribute to the development of this adipose tissue depot and coronary artery disease. This is an active area of investigation and the article in this issue of *AIDS* by Brener *et al.* [8] is timely and advances the field. This study takes advantage of coronary computed tomographic angiography (CCTA) imaging performed among patients in the MACS cohort. Using CCTA, the investigators evaluated coronary segments for presence or absence of any plaque and further characterized the plaque as calcified, noncalcified or mixed plaque. The Agatston calcium score was obtained as well. The study included over 900 patients, and is thus the largest CT imaging study to date in the HIV population. Importantly, the

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investigators measured EAT volume, along with visceral adipose tissue. Of note, there were small but significant differences in age between the HIV and non-HIV groups in the study by Brener *et al.*, but these differences were accounted for in adjusted analyses comparing EAT between HIV and controls.

One of the major findings of the study is that noncalcified plaque was increased in the HIV-infected vs. non-HIV-infected patients. This observation confirms and extends the observations from smaller prior studies. Noncalcified plaque was increased to a greater degree vs. non-HIV controls than was calcified plaque. Indeed, if anything, the prevalence of calcified plaque was less in HIV-infected patients vs. controls, although this difference did not reach significance. The study of Brener *et al.* [8] was limited to men, but recent studies in women show the same dichotomy, with even more striking differences in noncalcified plaque vs. non-HIV-infected controls [4]. Assessment of specific morphological features including low attenuation and positive remodeling indices was not performed by Brener *et al.*

A second major finding by Brener *et al.* relates to EAT, which was increased in the HIV group after adjustment for age and other factors. Prior studies, matching on age, race and BMI, have demonstrated increased EAT in HIV vs. non-HIV-infected patients [9]. Moreover, prior studies have demonstrated a relationship between EAT and carotid IMT [10], coronary artery calcium (CAC) score [11,12], CAC progression [13] and prior CVD events [14] in HIV-infected patients. In novel data, Brener *et al.* now demonstrate that EAT is significantly associated with increased prevalence of noncalcified plaque, and this relationship remains significant after adjustment for CVD risk factors among HIV-infected patients. The magnitude of this effect was such that an approximate 8% increase in EAT was associated with a 5–6% increase in prevalence of noncalcified plaque. Notably, the relationship fell out after adjustment for visceral fat in the HIV group but not the non-HIV group. EAT is significantly related to VAT, and thus adjusting for VAT affects this relationship in multivariate modeling among HIV-infected patients. Among those with any plaque present, EAT was most highly related to the extent of CAC among the HIV-infected patients. EAT was significantly related to a number of metabolic indices in addition to VAT, including glucose, insulin, and triglyceride concentrations, and duration ART.

What are we to make of these new data? First, they strongly suggest that HIV-infected men have a unique pattern of plaque on CTA, characterized by increases in noncalcified plaque. Second, they demonstrate increased EAT in HIV-infected men, which may relate to increased plaque as well as critical metabolic parameters. As the study by Brener *et al.* is cross-sectional, we do not know the sequence of development of EAT, nor how the

development of EAT relates temporally to metabolic abnormalities or plaque changes. However, the study raises a number of tantalizing questions for the field. Is the development of EAT, an ectopic adipose depot related to VAT, contributing to atherogenesis in the adjacent coronary vasculature? Does EAT relate specifically to high-risk morphology plaque or more to calcified plaque? If so, what is the mechanism of this effect? Will therapies aimed at reducing related VAT depots work to reduce EAT? Will strategies aimed at reducing atherogenesis, including statin therapy, affect EAT? Until longitudinal, randomized studies are completed, we will not know the answers to these important questions, but the study by Brener *et al.*, by extending our knowledge of this critical area, adds a new piece to the puzzle.

## Acknowledgements

### Conflicts of interest

The author has no disclosures to make relevant to this article.

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